Confirmation No. 9341

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

APPLICANT	: Patrick Bernardelli, et al.	EXAMINER	: Tamthom NGO Truong
SERIAL NO.	: 10/667,111	ART UNIT	: 1624
FILED	: September 17, 2003	PAPER NO	:
FOR	: New Spirotricyclic Derivatives And Their Use As Phosphodiesterase Inhibitors		

Amendment and Response

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Responsive to the Final Office Action dated January 12, 2006.

Amendments to the Claims begin on page 2.

Remarks/Arguments begin on page 6

A petition for a one month extension of time is also requested.

Amendments to the Claims:

1. (Canceled)

2. (Canceled)

3. (Currently Amended) A compound of claim ~~1~~ 18 wherein R^2 is $(C_1\text{-}C_4)$alkyl substituted with $-NR^4R^5$ or $-C(=O)NR^4R^5$; R^4 is $(C_1\text{-}C_6)$alkyl substituted with $-S(=O)CH_3$, $-NHC(=O)CH_3$ or $-C(=O)NR^7R^8$; R^5 is H or methyl; and R^7 and R^8 are the same or different and are H or methyl.

4. (Canceled)

5. (Currently Amended) A compound of claim ~~1~~ 18 wherein R^2 is $(C_1\text{-}C_6)$alkyl substituted with $-S(=O)R^3$; R^3 is $(C_1\text{-}C_6)$alkyl optionally substituted with one to three groups selected from $-S(=O)R^6$, $-SO_2R^6$, $-NR^7R^8$, $-OR^7$, $-NR'C(=O)R^7$, $-NR'SO_2R^7$; $-C(=O)NR^7R^8$; ~~or~~ and $-O-C(=O)NR^7R^8$; R^6 is $(C_1\text{-}C_6)$alkyl; and R', R^7 and R^8 are the same or different and are H or $(C_1\text{-}C_6)$alkyl.

6. (Currently Amended) A compound of claim ~~1~~ 18 wherein R^2 is $(C_1\text{-}C_6)$alkyl substituted with $-S(=O)R^3$; and R^3 is $(C_1\text{-}C_6)$alkyl, preferably methyl.

7. (Canceled)

8. (Currently Amended) A compound of claim ~~1~~ 18 wherein R^2 is $Q^1\text{-}Q^2\text{-}Q^3\text{-}Q^4$; Q^1 is a single bond; Q^2 is a saturated ~~4~~ 4- to 6-membered heterocycle comprising a nitrogen atom; Q^3 is $-CH_2-$; ~~and~~ Q^4 is a 5-~~membered.~~membered aromatic heterocycle comprising 2 nitrogen atoms, said heterocycle being optionally substituted with ~~methyl.~~methyl; the atom of Q^2 bound to Q^1 is a carbon atom; and the atom of Q^4 bound to Q^3 is a carbon atom.

9. (Currently Amended) A compound of claim ~~8~~ 18 wherein R^1 is -Cl or -F.

10. (Currently Amended) A compound of claim ~~8~~ 18 wherein m is 2.

11. (Currently Amended) A compound according to claim ~~8~~ 18 and selected from the group consisting of

5'-(2-[(2-amino-2-oxoethyl)amino]ethoxy)-8'-chloro-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one;

8'-chloro-5'-([methylsulfinyl]methoxy)-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one;

5'-(2-{[2-(acetylamino)ethyl]amino}ethoxy)-8'-chloro-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one;

8'-fluoro-5'-[3-(methylsulfinyl)propoxy]-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one;

8'-fluoro-5'-([methylsulfinyl]methoxy)-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one; ~~or~~and

8'-fluoro-5'-(2-{[1-(1H-pyrazol-3-ylmethyl)azetidin-3-yl]oxy}1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one.

12. (Canceled)

13. (Currently Amended) A method of ~~trating~~ treating a disease is selected from T-cell-related diseases, osteoporosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, leukemia, acquired immune deficiency syndrome (AIDS), allergy, dermatoses, psoriasis, atopic dermatitis, in a mammal comprising administering to said mammal in need thereof a compound of claim ~~1~~ 18.

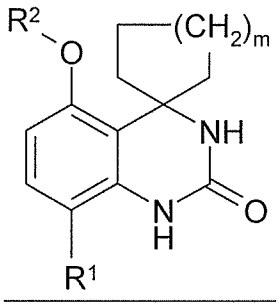
14. (Original) A method of claim 13 wherein said disease is asthma, allergy or atopic dermatitis.

15. (Original) A method of claim 13 wherein said disease is osteoporosis.

16. (Original) A method of claim 13 wherein said disease is cancer.

17. (Original) A pharmaceutical composition comprising a compound of claim ~~1~~–18 together with a pharmaceutically acceptable carrier, excipient, diluent or delivery system.

18. (New) A compound of formula (I):



wherein:

m is 1, 2 or 3;

R^1 is selected from CH_3, Cl, Br and F;

R^2 is selected from:

(a) Q^1-Q^2-Q^3-Q^4 wherein:

- Q^1 is a single bond or a linear or branched (C_1-C_6)alkylene group;
- Q^2 is a saturated 4 to 6-membered heterocycle comprising a nitrogen atom;
- Q^3 is a linear (C_1-C_4)alkylene group;
- Q^4 is a 5 or 6-membered, aromatic heterocycle comprising 1 to 4 nitrogen atoms, said heterocycle being optionally substituted with a methyl;
- the atom of Q^2 bound to Q^1 is a carbon atom; and
- the atom of Q^4 bound to Q^3 is a carbon atom;

(b) (C_1-C_6)alkyl, said alkyl group being substituted with a group selected from OR^4, $COOR^4$, NR^4R^5, $NRC(=O)R^4$, $C(=O)NR^4R^5$ and $SO_2NR^4R^5$, wherein:

- R is H or (C_1-C_6)alkyl;

- R^4 is $(C_1\text{-}C_6)$alkyl substituted with 1 to 3 groups selected from $S(=O)R^6$, SO_2R^6, $NR'C(=O)R^7$, $NR'SO_2R^6$, $C(=O)NR^7R^8$, $O\text{-}C(=O)NR^7R^8$ and $SO_2NR^7R^8$, wherein R^6 is $(C_1\text{-}C_6)$alkyl and R', R^7 and R^8 are the same or different and are selected from H and $(C_1\text{-}C_6)$alkyl; and
- R^5 is selected from R^4, H and $(C_1\text{-}C_6)$alkyl;

(c) $(C_1\text{-}C_6)$alkyl, said alkyl group being:

- substituted with 1 to 3 groups, preferably 1, selected from $OC(=O)R^{4a}$, SR^{4a}, $S(=O)R^3$, NR^aCOOR^{4a}, $NR^a\text{-}C(=O)\text{-}NR^{4a}R^{5a}$, $NR^a\text{-}SO_2\text{-}NR^{4a}R^{5a}$ and $NR^a\text{-}SO_2\text{-}R^3$, and
- optionally substituted with OH or OCH_3;

wherein:

- R^a is selected from H and CH_3;
- R^3 is $(C_1\text{-}C_6)$alkyl, unsubstituted or substituted with 1 to 3 groups, selected from F, CN, $S(=O)R^6$, SO_3H, SO_2R^6, $C(=O)\text{-}NH\text{-}SO_2\text{-}CH_3$, OR^7, SR^7, $COOR^7$, $C(=O)R^7$, $O\text{-}C(=O)NR^7R^8$, NR^7R^8, $NR'C(=O)R^7$, $NR'SO_2R^6$, $C(=O)NR^7R^8$ and $SO_2NR^7R^8$, wherein R^6 is $(C_1\text{-}C_6)$alkyl and R', R^7 and R^8 are the same or different and are selected from H and $(C_1\text{-}C_6)$alkyl;
- R^{4a} and R^{5a} are the same or different and are selected from H and R^3;

their racemic forms, their isomers or their pharmaceutically acceptable salts, solvates and hydrates.

REMARKS

I. Claim Status

Claims 3, 5-6, 8-11, and 13-18 are pending upon entry of the present amendment.

Claims 1, 2, 4, and 7 have been canceled.

Claims 3, 5-6, 8-11, and 13 have been amended.

New Claim 18 has been added.

Applicant has submitted herewith new Claim 18 which represents amended Claim 1 which has been amended to define the group Q^1-Q^2-Q^3-Q^4 to include the subject matter of original Claim 7. New Claim 18 also further defines the first set of possible substituents on the (C_1- C_6)alkyl group to those found in original Claim 2. Claim 18 further includes language to define a second set of possible substituents on the (C_1- C_6)alkyl group to those found in original Claim 4.

II. Rejection /under 35 U.S.C. § 112, Second Paragraph

Claims 1-10 and 13-17 remain rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, it was alleged it was unclear which set of substituents was intended for the alkyl or R^2 in Claim 1. Applicants have canceled Claim 1 and are submitting new claim 18 which includes amendments to the original Claim 1 to more clearly define the subject matter which Applicant regards as the invention. Specifically, the groups (b) and (c) as set forth in a new Claim 18, clearly define two separate lists of possible substituents for R^2 when it represents (C_1- C_6)alkyl. Applicants respectfully submit that there is no overlap between these substituents in each group in newly presented Claim 1. In view of newly submitted Claim 18, Applicants respectfully request that this rejection be withdrawn.

III. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 13-16 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Specifically, it was alleged in the Office Action that even though the specification is enabling for the treatment of AIDS (or HIV

infection), it does not reasonably provide enablement for the treatment of T-cell related disease, osteoporosis, chronic obstructive pulmonary disease (or COPD), asthma, cancer, leukemia.

Section 112, first paragraph, is satisfied where a specification contains a written description of the manner and process of *making and using* the subject invention in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same. Pages 10-24 clearly provide sufficient written description of the manner and process of both making and using the compounds of the present invention. It is further stated in the Office Action that even though Applicants cited several references linking PDE7 to allergy and asthma, T-cell mediated disease, dermatoses, cancer and leukemia, and osteoporosis, that because the cited references did not reveal a compound of spiro-quinazoline chemo type to treat those diseases, and that those references do not overcome the enablement rejection. Applicants respectfully submit that the literature references previously provided together with other literature cited in the application, and the support in the specification, provide sufficient guidance to one of skill in the art for a link between PDE7 inhibitors of the present invention and the claimed diseases/disorders.

It is further stated in the Office Action that the rejection of Claims 13-16 under 35 U.S.C. § 112, first paragraph, is maintained as the specification allegedly does not provide sufficient guidance in terms of *in-vivo* data for the treatment of many disease recited in Claims 13-16. Applicants respectfully submit that *in-vitro* or *in-vivo* data can be used in support of an asserted utility. In fact, the M.P.E.P. states that data reasonably correlated to specific therapeutic or pharmacological utility "almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process." M.P.E.P. § 2107.03(3). Based on the six examples the biological activity of the six examples set forth in the specification, and the utility of PDE7 inhibitors as disclosed in both the specification and the previously submitted references, one of ordinary skill in the art would expect that the compounds of formula I would have the claimed utility. Based on the above, Applicants respectfully submit that Claims 13-16 are fully enabled to one of ordinary skill in the art and Applicants respectfully request that this rejection be withdrawn.

IV. Double Patenting

Claims 1-11 and 13-17 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 1 and 3-26 of copending Publication No. 2004/0214843 A1. As Publication No. 2004/0214843 A1 is pending, Applicants defer responding to this rejection until any claims in the pending application is granted.

V. Supplemental Information Disclosure Statement

Applicants submit herewith a Supplemental Information Disclosure Statement. Applicants respectfully request consideration of the references identified in the enclosed Supplemental Information Disclosure Statement and further request that all references cited therein be printed on the face of the patent upon grant of the present application.

VI. Conclusion

In view of the amendments and remarks made above, Applicants believe that this application is now in condition for allowance. Reconsideration and allowance of Claims 3, 5-6, 8-11, and 13-18 is respectfully requested.

The Commissioner is authorized to charge any fee or credit any over payment in connection with this communication to our Deposit Account No. 23-0455.

Respectfully submitted,

Dated: 5/11/06

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